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Review In Mucoadhesive Bio-Flexy Film For Translabial Mucosal Drug Delivery

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ABSTRACT

The translabial mucosal drug delivery provide a significant application in release of drug by increasing bioavailability , the permeability of mucosa must be considered in the formulation of dosage form . Since a sustained drug release can be assure only if dosage form remain in contact with site of application for prolong time .the mucoadhesive bond formed of polymer and mucous substrate. The physical characteristics also be considered as factor influencing the mucoadhesion bond. The main aim of this study is to learn the translabial mucosal system behavior with bioflexy film .(Guava), Punica granatum (Pomegrante), Vitis vinifera (Grapes), Manilkara zapota (Chikoo) and Colocasia esculenta (Arbi)showed in-built ability as a novel film former as well as a mucoadhesant. The use of labial route as a mucoadhesive site is proved by study. The labial mucosa is an innovative site for mucoadhesion and can be used for drug delivery.

Keywords: Bio-flexy films, Biopolymers, Mucoadhesion, Labial mucosa.

INTRODUCTION:

Translabial drug delivery system defines a delivery system in which the absorption of drug moiety occurs via lips or mucosal membrane. Hence, there are many benefits of the system over the other route of drug delivery such as oral route in which there are certain dilemmas i.e., first- pass metabolism and GI degradation, which ultimately reduce the bioavailability of some drugs[1]. Whereas due to the ideal characteristics of labial mucosa, it has become an attractive fact towards the drug delivery system which includes many advantages like bypass of first-pass metabolism, prevent from digestive enzymes and rapid action of suitable drugs. As lips are those parts of the body of human being which are the most delicate and made up of thin layer. These are mainly composed of muscles, mucosa and skin, but there is no any bone and structure in its composition[1,2].

1.1. Translabial Drug Delivery System:

It is commonly known that lips make the external part of the mouth of living organisms as well as form the entrance of oral route for in-taking the food and other substance along with the production of voice. Due to the rich blood supply, lips appear to be red which consist then tissues below and also have less number of melanocytes than the individuals who have more melanocytes. Lips have dual properties, these provide both local and systematic effect when drug is applied on lips[2].

After seeing ideal characteristics of lips, it has been found that lips have an essential role in the formulation of translabial drug delivery system. Therefore, this system has distinct pros which include highly acceptable by patient, quick onset of action both locally and systematically due to

rich blood vessels, low dose, less chances of toxicity and less frequency of dose. It is considered that in near days, this system will soon flourish in drug's development[3].

A. Labium Anatomy:

As lips are found externally and visible part of animals and human beings which also surround the cavity of mouth[4, 5]. Lips are composed of various subcutaneous tissue, muscle fibers, epidermis and mucosa which are responsible for the flexibility of lips. Moreover, lips are surrounded by skin externally whereas by mucus membrane from inside these consist labial mucosa which is a part of oral mucosa and made up of buccal, palatal, gingival and lingual mucosa[6, 7].

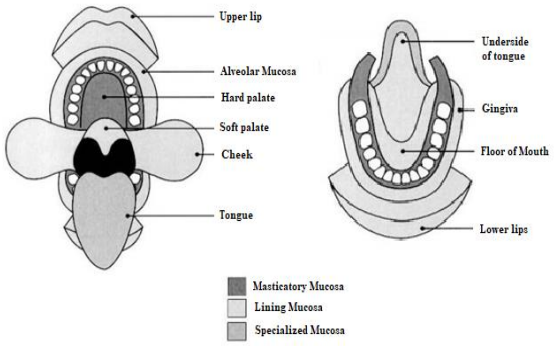

Fig. 1: Representation of the Schematic Different Linings of Mucosa in Mouth

B. Labium Histology:

The upper lip which is also known labium superiors, began from the nose to nasolabial folds and finally reach to the end of vermillion borders inferiorly. The internal surface of lips is made up of stratified squamous epithelium and is none keratinized. The outside surface of lips is composed of stratified squamous keratinized epithelium while the lips are made up of stratified squamous non-keratinized epithelium that is confronting an internal location of lips. The vermillion border lies between these two environments, that is, internal and external of lips. It also contains numerous arteries which are near to the surface of lips[3, 6, 8]

Blood Supply: External carotid artery contains various skin branches and it is a facial artery which is responsible to supply the blood to the lips through superior and inferior branches[9, 10].

Nerve Supply: The fifth cranial nerves of maxillary and mandibular branches provides the sensory stimulation to the lips. The sensory innervation are provided by the branches of mandibular nerve via a mental nerve branch to the lower lip innervation of lip. Whereas the sensory stimulation to the upper lip is received by the branches of maxillary nerve via infra- orbital nerve[11].

Muscles Supply: Lips with acting muscles are the part of facial muscles and these muscles are emerged with the mesoderm of the second pharyngeal arch. Therefore, it is delivered by the 7th cranial nerve of the second pharyngeal arch. The facial muscles are innervated with specialized members of panniculus carnosus that have attachment with dermis and hence, overlying skin is wrinkle.

Lymphatic Drainage: There is a unilateral lymphatic drainage in the upper lip which attaches and makes five major trunks that pass to the ipsilateral sub-mandibular nodes along with other drainage that also lead to the per parotid lymph nodes. The lymphatics which are attached to lower lip form five major trunks that further lead to bi-lateral submental nodes via central lip and by uni-lateral sub-mandibular lymph nodes through the lateral lip. Lips have first echelon nodes which are the submental, submandibular and parotid lymph nodes[12].

Sensory Innervations: Sensory innervations are originated from the fifth cranial nerve of the maxillary and mandibular branches. These nerve which is known as an infraorbital, is a terminal branch of the maxillary nerve that supplies to the upper lip and these nerve has infraorbital foramen 4-6mm under the inferior orbital rim on a vertical line which passes down from the medical limbus of iris. The nerve passes under the levator labii superioris and superficial to the levator angulis oris to innervate the upper lip.

Labial Mucosa Secretion: Labial mucosa is made up of epithelial, lamina propria and also from muscularis mucosa. The epithelial is very thin and non-keratinized. There is a long slender papillae of the lamina propria but also there is some wide ridges and dense connective tissue along with elastic fibers. The submucosa contains minor salivary glands and also it is attached to underlying muscles. The mucus is glassy and glutinous which is secreted by the vesicles inside the epithelial cells, and produce a thin, continuous gel blanket that adhere to the surface of mucosa epithelial[12,13].

Table 1: Comparison of Different Absorption Site of Mucosa:

Absorptive Site	Estimated Surface Area	Percent Total Surface Area	Local pH	Mean Fluid Volume	Relative Enzyme Activity	Relative Drug Absorption Capacity
Buccal	0.01 m^2	0.01	5.8-7.6	0.9	Moderate	High
Stomach	0.1-0.2m^2	0.20	1 - 3	118	High	High
Small Intestine	100 m^2	98.76	3 - 4	212	High	High
Large Intestine	0.5-1.0m^2	0.99	4 - 6	187	Moderate	Low
Rectum	200-400cm^2	0.04	5 - 6	-	Low	Low

1. Protection:

It results particularly from the hydrophobic property of mucus.

2. Barriers:

The mucus layer affects the absorption of drugs in the tissues, which in turn affects the bioavailability of the pharmaceutical drugs.

3. Adhesion:

Mucus having strong cohesion nature due to which it retain to the epithelial cells and helps in retaining of the mucoadhesive dosage forms.

4. Lubrication:

Mucus moisten the mucosal surface, so it shows an effective lubrication to mucosa and prevent drying.

5. Bioadhesion:

The mucus at physiological pH containing a significant negative charge because it contain sulphate and sialic acid residues. The negative charge plays an important role in the bioadhesion.[14,15]

C. Properties & Function of Lips skin (labial mucosa):

There are innumerable properties & functions of lips in order to make it different from other organ of body. They are as follows:[16]

- They are responsible for keeping unwanted objects out of the mouth.
- Lips have red appearance because of blood vessels which are visible from the thin skin of the lips and absence of pigments..

D. ADVANTAGES AND DISADVANTAGES OF TLDDS:

Advantages:

- It has no problem in the administration of dosages form as well as it can easily remove from the site of application.
- The application of dosages form has local, systemic and site specific action for a longer duration of time.

Disadvantages:

There are many complications with this route which are as follows:

- Drugs can be incompatible with the pH of labial mucosa that can be produce irritations with unpleasant taste and odor.
- Due to small area and little amount of drug, the dose is limited at the site of action. Therefore, APIs should contain in high potency so that therapeutic efficacy can be obtained without loss of dose..

E. Labial Mucosal Permeation Enhancers:

For labial mucosal various compounds have been used as a permeation enhancers to enhance the permeability of pharmaceutical drugs through the labial mucosa. There are various compound such as Cyclodextrin, Menthol, Benzalkonium chloride, Dextran sulfate, Polysorbate 80, Polyxyethylene, Lauric acid, Sodium EDTA, Sulfoxides, Sodium lauryl sulfate and Sodium glycodeoxycholate are used as a permeation enhancers in the translabial mucosal drug delivery.[17]

The permeation enhancers act by various mechanism such as altering mucus rheology by reducing the viscosity of the mucus or saliva, enhancing the fluidity of lipid bilayer membrane by changing the intracellular lipid packing through interaction between lipid and protein compounds, acting on the components at close-fitting junction through acting on desmosomes, overcoming the enzymatic barrier by preventing the several peptidases and proteases present in the mucosa and increasing the thermodynamic activity of pharmaceutical drugs by increasing the solubility and the partition coefficient of the drug to resulting better absorption of the drugs[18, 19]

F. Buccal Route of Drug Absorption:

The transport of drug through the oral mucosa occur by two pathways namely: paracellular route and transcellular route. Both the routes can be used simuntaneously but preferably one route is preferrered depending upon the physcochemical

properties of drug. When intracellular space and cytoplasms are hydrophilic in nature, then in this environment lipophilic compound will have low solubility. The cell membrane composed of lipophilic compounds then hydrophilic compound will permeate difficultely through this membrane due to low partition coffecients. Therefore, in this sense the intracellular space act as a main transport barrier for the transporting hydrophilic drug. Since the oral epithelium is stratified and solute permeation may include in a combination of these two routes[20, 21].

The permeation of drug through sweat ducts, hair follicles and sebaceous glands which collectively known as shunt route, is not possible due to the absence of hair follicles and sweat ducts in vermillion zone of labial mucosa [15,22, 23].

1.2. LABIAL MUCOADHESION OR BIOADHESION:

The term bioadhesion represents the bond between any two different biological surfaces or else a bond between the biological surface and synthetic surface. But, in the adhesive drug delivery, bioadhesion describes the adhesion between the polymer (either synthetic polymer or natural polymer) with soft tissues or gastrointestinal mucosa. When the bond is generated with mucus, then term mucoadhesion can be used as synonymously adhesion. Mucoadhesion is used as a term to define a phase in which two components, one is if natural origins held together for a longer duration of time with the help of interfacial forces. Commonly, bioadhesion is defined as a term which widely includes adhesive interactions to any naturally derived substance and mucoadhesion can be defined as the development of bond with mucosal surface[16, 24, 25].

Mucoadhesion drug delivery system includes various ways of drug delivery systems, they are as follows:

- Buccal drug delivery system
- Vaginal drug delivery system
- Rectal drug delivery system
- Oral drug delivery system
- Nasal drug delivery system
- Ocular drug delivery system

A. Mucoadhesive Drug Delivery System:

It is defined as the system in which material that binds to the mucous layer of the membrane. Different type of polymers are used for the systematic delivery of the drugs as a different dosage form for the mucoadhesive drug delivery of system are tablets, patches, tapes, films and powders etc. For the appropriate bioadhesive in the formulations is the pharmaceutical buccal patches. The various polymers are used in the formulations are agar, chitosan, acacia, guar gum, hydroxyethyl cellulose, hydroxyl propyl cellulose, sodium alginate and polyvinyl alcohol (PVA). The strong interaction between the mucous layer and the biomaterials results in the residence time and increase contact time. Polymer like guar gum was determine by using *ex- vivo* mucoadhesion study (shear stress measurement and detachment force measurement methods). *In-vitro* bioadhesion strength study and optimize drug release profile of the polymer determine by using a natural hydrophilic polymer (such as guar gum) and combinations of other polymers which is used to preparation of matrix films[14].

B. Mechanism of Mucoadhesion:

There is not yet a complete mechanism understanding available that how or why certain molecules are attached to the mucus surface, few steps are accepted in the process at least for solid system. There are certain theories which are proposed to comprehend the process for fundamental mechanism of adhesion. Firstly, mucoadhesion should have the capability to spread on the substrate in order to forms the close contact and increasing in surface contact promotes the diffusion of its chain in the mucus. The attraction forces and repulsion forces are a complexity in the mucoadhesion, and for successful adhesion, attractions should be controlled over it.[24,25]

C. Theories of Mucoadhesion:

- Electronic Theory:
- Absorption Theory
- Diffusion Theory
- Wetting Theory
- Cohesive Theory
- Fracture Theory
- Mechanical Theory

D. Mucoadhesive Polymers:[26]

A mucoadhesive polymers which is used for a mucoadhesive drug delivery system should have the following properties such as:

- These polymer should be non-toxic and non-absorbable.
- These polymer should be nonirritant and preferably economic.

a. Classification of Mucoadhesive Polymers: Mucoadhesive polymers classified into various classes based on their source, aqueous solubility, charge and potential mucoadhesive force.

- **Based on Source**

a) Natural Source

Such as: Agarose, Chitosan, gelatin, Gums (sodium alginate, xanthan guar and pectin).

b) Synthetic Source

Such as: Cellulose derivatives [Methyl Cellulose (MC), Carboxymethyl Cellulose (CMC),

c) Others source

Such as: Polyoxyethylene, PVA, Poly vinyl pyrrolidone (PVP), Thiolated polymer.

- **Based on Aqueous solubility**

a) Water Soluble

Such as: Carbopol, Hydroxyethyl Cellulose,

b) Water insoluble

Such as: Chitosan, Ethyl cellulose, Propyl cellulose and polycarbophil.

- **Based on Charge**

a) Cationic charge

Such as: Amino dextran, chitosan, (DEAE) - dextran, TMC.

b) Anionic charge

Such as: Chitosan-EDTA, Carbopol (CP),.

c) Non-ionic charge

Such as: Hydroxyethyl starch

- **Based on Potential Mucoadhesive forces**

a) Co-valent bond

Such as: Cyanoacrylate

b) Hydrogen bond

Such as: Acrylates [hydroxylated methacrylate,

c) Electrostatic interaction

Such as: Chitosan

E. Factors Affecting Labial Mucoadhesion:[25]

a. Molecular Weight
b. Flexibility of Polymer Chain
c. Cross-Linking Density
d. Hydrogen Bonding Capacity
e. Hydration
f. Charge
g. Initial Contact Time
h. pH at Mucoadhesive to Substrate Interface

F. Evaluation Parameters of Mucoadhesive Polymers:[27]

The mucoadhesive polymers evaluated by both *in-vitro* and *in-vivo* study.

1. ***In-vitro/ ex-vivo* study:** For studying the *in-vitro* or *ex-vivo* study various parameters are evaluated for mucoadhesive polymers. These parameters are:

- Determining tensile strength
- Determine shear stress
- Adhesion weight method
- Fluorescent probe method

2. ***In-vivo* study:**

- Use of radioisotopes
- Use of pharmacoscintigraphy
- Use of EPR (Electron paramagnetic resonance) oximetry
- Isolated loop process

Advantages of Mucoadhesive Drug Delivery System:

- If the pharmaceutical dosage form resides on the site of action for prolong time, it enhances the bioavailabilty.
- More access of drug at the site of action, rapid onset action.

Disadvantages of Mucoadhesive Drug Delivery System:

- There is one major complexity to screen the drug suitability for administration is the lack of good model in vitro.
- Due to prolong time to contact at the site can cause local ulcerous effect.

1.3. Limitations of Translabial Drug Delivery System:[25]

- Some drugs create problems which is having unpleasant odour and unpalatable taste.

- For translabial drug delivery system, cannot eat or drink after labial admistration of drug and some amount of drugs may be swallowed with saliva

1.4. Dosage Form: BIO-FLEXY FILMS:[28]

Recently, flexy-films are the most advanced pharmaceutical dosage form for translabial mucosal route. Mucoadhesive biofilms may be referred adhesive tablets in their flexibility and comfort. Bio-flexy films as a dosage form in the pharmaceutical department as novel, patients friendly and convenient products and it is also act as a controlled and target specific drug delivery. An ideal bio-flexy films must be flexible, soft and adequately strong to tolerate cracking due to pressure from mouth activities. It must also shows good bioadhesive strength to be stable and retained at the site of action for the required duration of action.[29,30]

For the formulation of bio-flexy films biopolymers play a vital role. Biopolymers terms are polymers which is formed by living organisms and it contains monomeric units that are covalently bonded to the formation of a larger structures. Biopolymers are classified in three different classes based on their differing monomeric unit and on the bases of the structure of the biopolymer formed:

1. Poly-nucleotides: these polymers containing 13 or more than 13 nucleotide monomers.
2. Poly-peptides: these polymers containing amino acids
3. Poly-saccharides: these polymers are often linear bonded polymeric carbohydrate structures.

There is a main difference between the polymers and the biopolymers is found in their structure. All the polymers are made up of repetitive units called monomers.

Other excipients such as dextrose is widely used in the formulation of bio-flexy films it is used as a plasticizer and provide desired flexibility to the bio-flexy films.[30]

Conclusion:

Research evidence proof that the translabial drug delivery system gives better effect with bio flexy film. It also reduces the side effect of drug with other routes. This system is potentially novelistic for the systemic designing. And the above formulation preparation will become quite interesting. And due to ideal characteristic of labial mucosa it's an attractice fact for drug delivery system which contain advantages like rapid action, duration of action and safety from digestive enzyme.

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